ACC.15
TCT@ACC-i2 | innovation in intervention

A1542
JACC March 17, 2015
Volume 65, Issue 10S

Pulmonary Hypertension and Venous Thrombo-embolic Disease

THE NON-PROSTANOID PROSTACYCLIN RECEPTOR AGONIST ACT-333679, THE ACTIVE METABOLITE OF SELEXIPAG, IS CHARACTERIZED BY LOW BETA-ARRESTIN RECRUITMENT AND RECEPTOR INTERNALIZATION ACTIVITY

Poster Contributions
Poster Hall B1
Saturday, March 14, 2015, 10:00 a.m.-10:45 a.m.

Session Title: Epidemiology and Pathogenic Pathways in Pulmonary Arterial Hypertension
Abstract Category: 24. Pulmonary Hypertension and Pulmonary Thrombo-embolic Disease
Presentation Number: 1110-174

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Background: Prostacyclin receptor (IP receptor) agonists, which are used in the treatment of pulmonary arterial hypertension (PAH), increase cytosolic cAMP levels and thereby cause pulmonary vasodilation and inhibition of smooth muscle cell proliferation. Tachyphylaxis following repeated exposure to agonists may occur via receptor desensitization/internalization. This study analyzed β-arrestin recruitment - a measure of receptor uncoupling - and IP receptor internalization in response to ACT-333679, the active metabolite of the experimental PAH drug selexipag.

Methods: Recombinant IP receptor expressing CHO cells were used to characterize the prostacyclin analogs iloprost, beraprost, treprostinil and the non-prostanoid IP receptor agonist ACT-333679 with respect to their potency and efficacy to activate adenylate cyclase, to recruit β-arrestin, and to internalize IP receptors. We employed cAMP accumulation assays, β-arrestin enzyme fragment complementation assays, immunofluorescence microscopy, and flow cytometry.

Results: In cAMP accumulation assays, all four compounds acted as full agonists (Emax ~ 100%) with EC50 values between 0.1 and 1.1 nM. In β-arrestin recruitment assays intrinsic EC50 values were between 35 and 212 nM. The non-prostanoid agonist ACT-333679 displayed lower maximal efficacy in recruiting β-arrestin (Emax=40%) compared to the prostacyclin analogues iloprost, beraprost and treprostinil (Emax= 100, 90 and 67%, respectively). Lower β-arrestin recruitment efficacy translated into a lack of IP receptor internalization in ACT-333679-treated cells, even at high agonist concentrations. In contrast, iloprost, beraprost and treprostinil induced strong receptor internalization, as shown by immunofluorescence microscopy and flow cytometry.

Conclusion: ACT-333679, the active metabolite of selexipag, while retaining full efficacy in inducing cAMP responses, does not lead to IP receptor desensitization and internalization like the classical prostacyclin analogs and might therefore not result in tachyphylaxis upon multiple dosing in vivo.